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Review Article

Cardiac Metastasis in Diffuse Large B Cell Lymphoma: Article Review

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Abstract

Diffuse Large B Cell Lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma that metastasizes to the heart. It was considered rare and was detected mainly at autopsy, but the prevalence has risen in recent times. The prognosis is poor if left untreated. Although most cases respond to chemotherapy well, the treatment can be associated with life-threatening complications including ventricular fibrillation, pulmonary embolism, and cardiac rupture early after chemotherapy. Little data is available regarding the optimal approach. A reduced chemotherapy dose was reported in several cases to decrease the risk of complications however, the inadequate treatment of cancer remains a concern. Moreover, chimeric T-cell (CAR-T cell) therapy resulted in significant improvement in other cases. In this manuscript, we intend to explore the symptoms and treatment of DLBCL with cardiac metastasis and the resulting outcomes. Our study includes 29 published cases older than 18 years with DLBCL who were diagnosed with cardiac metastasis. In 50% of cases, cardiac metastasis was detected at the initial presentation and diagnosis of lymphoma. Shortness of breath was the most common manifestation. 80.7 % of the cases underwent isolated chemotherapy and signs of improvement were reported as early as 1 month. Reduced chemotherapy dose was performed just in one case for the first cycle. Five out of 29 patients expired despite treatment. Arrhythmia was the cause of death in one patient. CAR-T cell, which was performed in 3 cases with resistance to chemotherapy, was associated with favorable outcomes.

Keywords: Secondary Diffuse Large B cell Lymphoma, metastasis, Cardiac lymphoma, RCHOP regimen

Introduction

Secondary cardiac lymphoma is relatively common. Approximately, 20% of patients passing from lymphoma have been found to have cardiac involvement, which is usually diagnosed at autopsy [1]. Most cardiac lymphomas, whether primary or secondary, are of B-cell lineage, of which non-Hodgkin's lymphoma accounts for 80% of cases [2]. Diffuse large B cell lymphoma (DLBCL) is the most common subtype [3]. Cardiac metastasis develops through three major routes: direct extension of a mediastinal tumor to the heart which usually involves pericardium, retrograde lymphatic spread, and diffuse interstitial-perivascular spread which can lead to an epicardial and myocardial metastasis, respectively. The metastasis can involve all heart structures, most commonly the right atrium [5]. The presentation varies depending on the location, size, and degree of invasion of the tumor, with symptoms including chest pain, dyspnoea, acute heart failure, superior vena cava (SVC) syndrome, embolic phenomenon, and arrhythmia [4]. The prognosis of cardiac lymphoma is poor due to the progressive nature of the disease and treatment-associated

complications. The mortality rate is 8.5% to 25% if left untreated [5]. Early diagnosis and proper treatment can enhance survival rates, and different strategies and adjuvant treatments can be offered [6]. Although most DLBCL cases respond to chemotherapy, severe complications have been documented following treatment. As little data is available regarding novel treatments, individualized treatment is considered to minimize the risk of complications and to achieve the best response. In this manuscript, we intend to explore the symptoms and treatment of DLBCL with cardiac metastasis and the resulting outcomes.

Material and Methods

A systematic literature review was performed on Google Scholar and PubMed. The keywords "Secondary DLBCL" and "cardiac involvement" were used. Case reports written in English, published between 2020 and 2023, involving adults aged more than 18 with diffuse large B cell lymphoma and cardiac metastasis were included. The exclusion criteria were papers in languages other than English, pediatric population, primary cardiac lymphoma, and articles requiring a subscription. The final analysis included 29 case reports.

Results

The median age of cases was 50.72 years. 48.2% of the cases were male. In about half of the cases, the diagnosis of cardiac lymphoma was made during the initial presentation and diagnosis of lymphoma. Although, it was reported even years after the primary lymphoma diagnosis. Among those cases with a primary site of lymphoma documented, mediastinal lymphoma was the most common primary site (30 %) followed by the abdomen. Other primary sites were the uterus, testicle, kidney, and adrenal.

Cardiac lymphoma presentations varied from no symptoms to cardiogenic shock. About one-third of the patients presented with shortness of breath. Cardiogenic shock was reported in 2 cases. Arrhythmias including complete heart block, ventricular tachycardia, sick sinus syndrome, and atrial flutter were reported as the initial presentation in 3,2,1, and 1 of the cases, respectively. One patient manifested with syncope. Isolated right-side metastasis was 3 times more common than the isolated left heart (15 versus 5). The right atrium was involved in 50 % of cases. Pericardial metastasis or pericardial effusion was seen in 7 cases. Interatrial metastasis was reported in 2 cases. In most cases, more than 1 imaging modalities were used for diagnosis. Transthoracic echocardiography was performed in 13 cases and among 5 of them it was the only imaging that was used. Isolated chest CT was done in 2 cases. Cardiac biopsy was performed in only 2 cases for confirmation.

Almost all patients underwent chemotherapy. Reduced first-dose chemotherapy was mentioned in one case. In 3 cases CAR- T cell therapy was performed in addition to chemotherapy. Radiation therapy was done in one case. Follow-ups were performed at different times ranging from after the 2nd chemotherapy to 2 years. PET/CT and FDG-PET were the most common modalities used for follow-up (9 cases). The resolution of the tumor was noted as early as after the second chemotherapy. In all 3 patients with complete heart block, a pacemaker was placed. Pacemaker interrogation was performed in 2 cases which revealed a decreased pacing burden from 100% to 80% after the 2nd dose of chemotherapy and 1% ventricular pacing after 1 month. Five patients died. Pneumonia, multi-organ failure, and arrhythmia were documented as the causes of death (Table 1).

Author	Year of publication	Gender	Age	Time of diagnosis	Initial presentation of cardiac metastasis	Initial Site of Cancer	Imaging for Diagnosis	Treatment	Site of metastasis	Follow up	Finding	Follow up imaging
Yang, et al. [2]	2023	M	59	12 months after initial diagnosis	Refractory dyspnea and bilateral pleural effusion	mediastinal lymph node and peripancreatic mass	Contrast TTE	chemo, NK cell immunotherapy, Transplant	Pulmonary vein and LA	Death after 6 months due to severe pneumonia	N/A	N/A
Disley, et al. [7]	2023	F	42	Initial	Rt side HF, Flutter	diffuse	Cardiac MRI	High dose Chemo	RA, RV, TV	7 months	Resolved	N/A
Chen, et al. [8]	2023	M	77	Initial	VT	mediastinal and submandibular	PET/CT	Chemo	RV	3 months	Decreased uptake and resolved VT	PET/CT
Choudhry et al. [9]	2023	M	58	Initial	Chest tightness	Inguinal mass	Chest CT and TTE	Chemo	RA, RV	5 months	Complete resolution	Cardiac MRI
Ng, et al. [10]	2023	M	37	After ASCT	None	N/A	PET/CTCMR	ChemoCAR-T	LV	1 month	Near complete metabolic response	FDG PET/CT
Ng, et al.[10]	2023	F	30	N/A	Chest Pain, SOB and palpitation	Mediastinal	PET/CT,CMR	ChemoCAR-T	Pericardium	1 month	Improvementin uptake	FDG PET/CT
Wang, et al. [5]	2023	M	57	8 months after chemo, radiation	Facial swelling and SOB	mediastinal	Chest CT,TTE	Chemo, Radiation	RA, RV	N/A	TTE	Complete regression
Sabir, et al.[11]	2023	F	93	N/A	Respiratory distress	Reishter transformation	TTE andchest CT	None	Pericardial effusion	N/A	NA	N/A
Arshad, et al. [12]	2023	F	41	Initial	CP, SOB	Supraclavicular	TTE	Chemo	RA, RV, Tricuspid annulus	1 year	Cardiac mass resolution and EF normalization	TTE
Bonilla, et al. [13]	2023	M	38	After chemo and SCT	N/A	N/A	FDG-PET	Chemo, transplant, CAR-T	N/A	1 month	Near complete resolution	FDG-PET
Akimana, et al. [14]	2022	M	49	N/A	N/A	Abd and testicular	Chest CT,TTE, TEE	Chemo	RA, RV.PA	Death after1st cure	N/A	N/A
Chen,et al.[15]	2022	F	42	Initial	Chest pressure	Mediastinal	Chest CT,TTE, CMR	Chemo	RA, RV, PE	3 months	Decrease in mass size	N/A
Borges, et al. [16]	2022	F	20	Initial	Progressive exertional dyspnea	Mesenteric	TTE, CMR	Chemo	RV, pericardium, Great vessels	Death dueto multipleorgan Dys	N/A	N/A
Ishibashi, et al. [17]	2023	M	71	Initial presentation)	Chest pain with (Brugada pattern in dialysis	mesenteric, pancreas, lung, adrenal	TTE, Chest CT (Confirmed autopsy)	N/A	RA, RV, PE	Death	N/A	N/A
Birs, et al.[18]	2020	M	64	N/A	N/A	N/A	TTE, CMR PET	Chemo	RA	N/A	N/A	N/A
Sanders, et al. [19]	2022	F	62	Initial presentation	CHB and cardiogenic shock	Abd	Chest CT	prednisone followed bychemo	RA, RV, PE	28 days	NSR	ECG
Subramany AM, et al.[20]	2020	M	57	Subsequent	Dizziness and CHB	Abd	CMR, PET	Chemo	Interatrial and interventricular septum, AR, PV	1 month	1 % ventricular pacing	Pacemaker interrogation
Panareo, et al. [21]	2020	M	71	22 monthsafter initial	Dyspnea and SVC syndrome	Testicular	Chest CT,PET/ CT and biopsy	Chemo	RA and SVC, Rt jugular	After the 7th chemo	Complete remission	PET/CT
Celic, et al. [22]	2020	F	70	Initial	Syncope	Mediastinal, inguinal	TTE	Chemo	LV	N/A	N/A	N/A
Aldarzi, et al. [23]	2020	F	72	Initial	Fatigue and dyspnea CHB	Diffuse(Neck, chest, kidney)	TTE	Reduced 1stdose chemo	Interatrial septum	After the 2nd chemo	complete resolution of tumor decreased pacing from 100% to 80%	PET/CT Pacemaker check after6 months
Yunis, et al. [24]	2022	F	26	Initial	Facial and Rt upper limb swelling	Mediastinal, Pelvis	TTE	Chemo	RA, severePE	2 years	No abnormalities	PET/CT
Husain, et al. [25]	2021	F	22	Subsequent	none	cervical	FDG-PET, CMR	Chemo	LV	N/A	N/A	N/A
Tekinalp, et al. [26]	2022	F	61	subsequent	None	gastric	Chest CT,PET-CT	Chemo	Interatrial septum, IVC	3 months	N/A	N/A
Yamaji, et al. [27]	2023	M	65	In 1 year	Exertional dyspnea	multiple	Chest Ct	N/A	myocardium	Death Dueto arrhythmia	N/A	N/A
Papanastas tasiou,et al. [28]	2022	N/A	72	Initial	N/A	Adrenal	Chest Ct,PET/ CT	Chemo	RA, SVC	3 monthsafter 6th	Decreased infiltration	N/A
Tsugu, et al. [29]	2023	F	57	Initial	skip beats	Uterus	PET/CT	Chemo	RA	6 monthsafter chemo	Neg uptake	FDG-Pet/CT
Umair, et al. [4]	2022	M	47	Initial	Cardiogenic shock and VT	Kidney	ChestCTA, cardiacbiopsy	High dosechemo	LV	6 months	EF improved from 15 to 45	N/A
Kondo, et al. [30]	2020	M	85	Initial	Syncope, SSS	Mediastinal	Chest CT,TEE	Chemo	RA, LA,SVC	After 8thchemo 6 months	Decreasedmass size Pacing:0.4,N SR	Chest CT Pacemaker interrogation
Serin, et al. [31]	2020	F	45	3 months after normalPET	Chest pain	Diffuse	N/A	chemo	Pericardium	N/A	No sign of recurrence	PET/CT

Rt: right, TTE: transthoracic echocardiography, SSS: sick sinus syndrome, CHB: complete heart block, RA: right atrium, LA: left atrium, RV: right ventricle, LV: left ventricle, SVC: superior vena cava, IVC: inferior vena cava, PE: pericardial effusion, CAR-T: chimeric antigen receptor- T cell, TEE: transesophageal echocardiography, TTE: transthoracic echocardiography, N/A: not applicable, TV: tricuspid valve, NSR: normal sinus rhythm, Initial: initial presentation, VT: ventricular tachycardia, Abd: Abdomen,

Table 1: Characteristics of published cases.

Discussion

The available data regarding DLBCL with cardiac metastasis is scarce. In our study consistent with the other studies the median age was less than 55 years [32]. The majority of patients were female. As expected, right-side involvement was 3 times more likely than the left-side and the right atrium was the most common involved chamber. Consistent with previous studies, manifestations varied from asymptomatic to non-specific symptoms including shortness of breath and chest pain to severe symptoms such as cardiogenic shock and malignant arrhythmias with the predominance of shortness of breath [2,6]. In our study, cardiac involvement was diagnosed at the time of initial presentation in half of the patients, unlike the previous studies in which it was diagnosed at autopsy or the diagnosis was delayed. [6,32].

Various imaging modalities with district sensitivity and specificity have been introduced for the diagnosis of cardiac lymphoma. While ECG is not sensitive, echocardiography demonstrates a specificity and sensitivity of 95% and 90 %, respectively. It can reveal the characteristics of the tumors such as size, shape, mobility, location, and burden of involvement [33]. Computed tomography (CT) is excellent imaging that provides information about cardiac lymphoma in addition to the extracardiac structures, typically manifests as iso to hypo-attenuating mass. Positron emission tomography (PET) /CT is preferred over each modality because it provides more accurate information about the overall staging of lymphoma compared to CT alone, with superior anatomical resolution compared to PET alone [6].

The cornerstone of the treatment is chemotherapy. Chemotherapy was reported to be associated with increased survival from 1 month to 18 months [34]. The standard regimen includes rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) [16]. 63.2 % response to the treatment was reported in prior studies [3]. In our study, 21 patients underwent isolated chemotherapy which was associated with favorable outcomes leading to near-complete to complete resolution of the tumor, normalization of the ejection fraction, and resolution of arrhythmia. Furthermore, atrioventricular (AV) node conduction abnormalities were usually amenable to chemotherapy. The addition of high-dose prednisone, however, was associated with the resolution of persistent heart block after chemotherapy [19].

Since complications such as ventricular fibrillation, cardiac perforation, and massive pulmonary emboli can happen early after chemotherapy in patients with cardiac metastasis, reducing the chemotherapy dose and covering the affected part with a bovine membrane were preferred in a few cases [6]. The disadvantage of reduced chemotherapy doses is inadequate treatment. However, in our study reducing the first chemotherapy dose was performed in just 1 patient [23]. Arrhythmia was reported in 1 case as the cause of death. However, the time of arrhythmia was not documented. No cardiac rupture was reported among the cases.

Multiple therapies including radiation therapy, autologous stem cell transplantation, and chimeric T-cell therapy can be used in addition to chemotherapy. Radiation therapy was performed in 1 case after chemotherapy without significant complications [5]. In our study, three patients underwent CAR-T cell therapy which was associated with cytokine release syndrome but no further cardiotoxicity [10,13].

Conclusion

Cardiac metastasis in DLBCL is not as rare as was considered. Based on the studies, prompt and appropriate treatment can lead to improved outcomes. Currently, our knowledge regarding the best treatment and possible complications is little. The decision is made on a case-by-case basis to minimize the risk of complications. Further trials are needed to compare the efficacy and safety of reduced-dose chemotherapy versus regular chemotherapy and adjuvant therapies including CAR-T cell therapy.

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